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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,723	04/10/2006	Yigong Shi	112911.01901	2077

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
06/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,723	SHI ET AL	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-20,44 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-20,44 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/8/06 2/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 21-43, 45 and 47 have been canceled. Claims 1-20, 44 and 46 are pending and examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20, 44 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the condition wherein R1a is H, X is NH, J is CH, Y is H, methyl or isopropyl, R2 is

and R1 is methyl and diagnostic agents comprising said compounds, does not reasonably provide enablement for the condition wherein R1a is H, X is NH, J is CH, Y is H, methyl or isopropyl, R2 is

and R1 is ethenyl or pharmaceutical composition comprising any of said compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A)As drawn to the structures encompassed by the claims

The specification teaches that the instant compounds are peptidomimetics of the N-terminal tetrapeptide of the mitochondrial protein Smac/DIABLO which promote apoptosis in cells through a pathway involving the Inhibitor of Apoptosis Proteins and that these peptides bind to IAPs and offer improved pharmacological features as compared with the tetrapeptide. The specification provides a correlation between binding to an IAP relative to the binding of the tetrapeptide for the methylene-bridged compounds of the invention (page 40) and for the oxazole based compounds of the invention (page 41). In neither set of compounds is there a structural feature of the ethenyl required by the instant claims when R1a is H. The specification fails to provide a method of synthesizing such compounds requiring an ethenyl for R1 The compounds of the invention are multifunctional. The art teaches that presence of differing functional groups, and three dimensional configurations require different considerations as to protecting groups, and reactivity manifest in different synthetic strategies (Sierra and de la Torre, Angewandte Chemie, 2000, Vol. 39, pp. 1538-1559, especially pages 1544-1546, "Troublesome Protecting Groups"). Chemical structure heterogeneity including the presence of different heteroatoms on different three dimensional structures can radically alter the reactivity of any other atom within a molecule through inductive effects (page 1545, second column, lines 2-6 of the second full paragraph and lines 4-7 of the third full paragraph, resonance effects, acidity, basicity and steric hindrance (page 1552-1554), strain (page 1554-1557) or transition state crowding (page 1545, second column, second full paragraph, lines 2-6,, page 1546, second column, first full paragraph) and therefore can radically influence the reactivity with any given reagent contacted thereto. Sierra and de la Torre teach that a well-testing transformation can fail for complex reasons (Sierra and de la Torre, ibib, page 1540, first column, lines 9-11, page 1541, first column, lines 33-37, under the heading "Working Models that do not Work", page 1542, first column, lines 15-17, even

when supported by molecular mechanics calculations (page 1542, first column, lines 6-9) and what is seen as an innocuous alteration can cause a failure in a synthetic step (page 1542, second column, lines 9-12). Sierra and de la Torre teach that the presence of remote substitutions has unexpected influence over a chemical step (pages 1546-1548, under the heading "The Unexpected Influence of Remote Substituents") Sierra and de la Torre state that "As the complexity of intermediates increases, the number of variables involved in a simple transformation grow exponentially making predictions about the outcome of any given synthetic step on a highly functionalized intermediate, unreliable (page 1548, second column, lines 5-8 of the second full paragraph, page 1550, second column, lines 1-9 under the heading "The Trivial Functional Group Transformation"). Sierra and de la Torre conclude that the lack of predictability in so many cases and the very empirical nature of synthetic organic chemistry implies that the science is not fully developed (page 1548, second column, lines 13-16 of the second full paragraph). Sierra and de la Torre state that alternate routes can then be devised which circumvent a failed transformation (page1548, second column, lines 10-13 of the second full paragraph), however, the sum total effort of designing and redesigning represents undue experimentation to one of skill in the art, exemplified by Sierra and de la Torre as "the amount of effort devoted to simple transformations is still quite enormous" (page 1557, first column, lines 15-18). Thus it is concluded that due to the unpredictability of the art that one of skill in the art would be subject to undue experimentation in order to make the compound wherein R1a is H and R1 is ethenyl.

Further, the specification provides no data as to the binding of the ethenyl compound to IAP, In the event that said compound does not bind as well, or less well as the tetrapeptide, the specification fails to teach a use for said ethenyl compound and a use of a pharmaceutical composition comprising said compound (claim 44).

(B)As drawn to pharmaceutical compositions.

The specification teaches that the instant compounds are peptidomimetics of the N-terminal tetrapeptide of the mitochondrial protein Smac/DIABLO which promote apoptosis in cells through a pathway involving the Inhibitor of Apoptosis Proteins and that these peptides bind to IAPs and offer improved pharmacological features as compared with the tetrapeptide. In order for the instant compounds to function as pharmaceuticals, it would be necessary for said

compounds to penetrate cell membranes in order to bind to the IAP. The art teaches peptide motifs which provide peptides with membrane permeation ability (for example, Lin et al, Journal of Biological chemistry, 1995, Vol. 270, pp. 14255-14258). However, it is unclear how the presence of said motif on the compounds of the invention would alter the binding activity to IAPs. Given the lack of teachings and guidance in the specification regarding such issues as membrane permeability and modifications to impart membrane permeability to the extent that administered compounds would be in contact with the IAPs without the concomitant loss of IAP binding, one of skill in the art would be subject to undue experimentation in order to use the claimed compounds in a pharmaceutical compositions.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643